**REMARKS**

Claims 1-28 presently appear in this case. No claims have been allowed, although it is noted that only claims 10, 11 and 15-17 have been rejected over the prior art. The official action of April 10, 2001, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to the discovery that a complex of interferon and an IFN binding chain of the human interferon α/β receptor (IFNAR) will improve the stability and enhance the potency of the IFN. The complex may be a non-covalent complex, or the IFN and the IFNAR may be bound by a covalent bond or a peptide bond, either directly or through a linker.

Claims 10, 11 and 15-17 have been rejected under 35 U.S.C. §102(b) has anticipated by either Cohen or Yeda or Novick. The examiner states that the "isolated" language of claim 10 does not distinguish the product of Cohen, Yeda or Novick because, in the prior art, the complex is isolated from at least some of the components of the original mixture. As to applicants' argument about "consisting essentially of", the examiner states that applicants' argument has not been found to be persuasive because the definition on page 32 excludes



C

substitutions, deletions and additions, but does not exclude derivatives. These rejections are respectfully traversed.

The examiner accepts that the definition of the term "consisting essentially of" is governed by the definition in the present specification at page 32, lines 13-18, which state:

> The term "consisting essentially of", when referring to a specified sequence, means that additional flanking residues can be present which do not affect the basic and novel characteristic of the specified sequence. This term does not comprehend substitutions, deletions or additions within the specified sequence.

The examiner appears to believe that the term "excludes substitutions, deletions or additions" does not exclude derivatives. It is urged, however, that this is not true. The derivatives of the prior art are formed in the manner described in Yeda at page 7, lines 11-16, specifically the description:

> Briefly, 7 µg of IFN-α was labeled with 1 mCi of $Na^{125}I$ in the presence of 1 mg/ml of chloramine T (20 sec on ice), to a specific activity of $4 \times 10^7$ cpm/µg.

Claim 10 a) provides that the Type I IFN "has a sequence consisting essentially of the sequence of ... a native Type I IFN". The examiner states that this reads on $^{125}I$-derivatized native Type I IFN. However, $^{125}I$-derivatized IFN-α does not have the sequence of native Type I IFN because

those amino acids which have been converted to the $^{125}I$ salt are no longer native amino acids. Effectively, a $^{125}I$-derivatized amino acid residue has been substituted for the native amino acid, yet the definition of "consisting essentially of" explicitly excludes substitutions of amino acids within the native IFN sequence. The only exception to the exclusion of such derivatized substitutions is in the term "a salt or functional derivative of a)". However, the definition of functional derivatives as appearing on page 30 of the present specification includes the statement at lines 1-9:

> "Functional derivatives" as used herein covers derivatives which may be prepared from the functional groups which occur as side chains on the residues or the N- or C-terminal groups, by means known in the art, and are included in the invention as long as they remain pharmaceutically acceptable, i.e., they do not destroy the biological activity of the corresponding protein of the complex as described herein and do not confer toxic properties on compositions containing it or the complex made therefrom.

The examiner has conceded that the $^{125}I$ confers toxic properties on compositions. Thus, the $^{125}I$ IFN-α is not a functional derivative of IFN-α. As there is some overlap in the definition of "salt" (page 31 of the present specification) and "functional derivatives" (page 30 of the present specification), the term "salt" has now been deleted

from claim 10, insofar as the interferon is concerned. Of course, the inorganic salts and salts with organic bases and acid addition salts, defined on page 31, also fall within the definition of "derivatives which may be prepared from the functional groups which occur as side chains on the residues". The term "salt" is being deleted merely in order to make clear that any such salt must have the further requirement of "functional derivative" with respect to not conferring toxic properties.

In conclusion, $^{125}$I IFN-α is not Type I interferon with a sequence consisting essentially of the sequence of a native Type I interferon, as native amino acid residues of the native Type I interferon have been substituted by $^{125}$I salts of such residues. The term "consisting essentially of" explicitly excludes such substitutions. Furthermore, it does not fall under the language "functional derivative of a)" as the presence of $^{125}$I in such a derivative confers toxic properties and, thus, does not fall within the definition of "functional derivative".

In order to further clarify claim 10, the clause previously referred to as "e)" is no longer listed with a), b), c) and d), but is set forth as a definition of the Type I IFN, as opposed to a definition of the sequence. Thus, claim 10 now reads that the Type I IFN has a sequence consisting

essentially of the sequence of a), b), c) or d), or a functional derivative of a), b), c) or d). This was necessary because a functional derivative, as discussed above, does not have "a sequence consisting essentially of the sequence of" any of a), b), c) or d).

Thus, it has been shown that $^{125}$I-derivatized IFN-α is not a sequence consisting essentially of native IFN-α because $^{125}$I-substituted residues are not native residues but are substitutions for the native residues which are excluded by the definition of "consisting essentially of". It is further not a functional derivative of native IFN-α because it does not fall within the definition of "functional derivative" as discussed above. Thus, the present rejections must be withdrawn for these reasons. In addition, however, the rejection should be withdrawn because the term "isolated" is understood by those of ordinary skill in the art to mean that it is isolated to a degree that it is substantially free of any other protein. As explained in applicants' amendment of January 24, 2001, the prior art does not disclose isolated complex as there is always significant amounts of other protein present. Respectfully, it is inappropriate to take the position that anything which has undergone any degree of purification, presumably even a very slight degree, must be considered to be "isolated" because it is at least isolated

from something that was originally present. The term "isolation" is defined, for example, in the McGraw Hill Dictionary of Scientific and Technical Terms, Lapides, ed. (1976), p. 782, with respect to chemistry as:

> [CHEM] separation of a pure chemical substance from a compound or mixture; as in distillation, precipitation, or absorption.

As the complex of Yeda, Cohen and Novick is not a pure chemical substance, i.e., a pure protein complex separated from other proteins, it is not in isolation and cannot be considered to be "an isolated molecule". Reconsideration and withdrawal of these rejections on this ground as well are also respectfully urged.

It should be understood that in view of applicants' argument that a derivatized amino acid in an interferon protein is effectively a substituted amino acid which is precluded by the express definition of "consisting essentially of", it would be appropriate for the examiner to state in the reasons for allowance that the rejection over the prior art has been withdrawn in view of this argument. Applicants would then be precluded from interpreting the claim in any other way after the patent issues.

Claims 1-28 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite in the recitation of "Type I IFN biological activity". The examiner states that

the amendment limiting the claims to "agonist" activity is insufficient to limit the claims absent any specific teachings as to what activities are considered to be "biological activity". The examiner states that the teachings on page 33 refer to "receptor agonist activity" but are silent with respect to "biological agonist activity".

The claims have now been amended to change the term "biological agonist activity" to read "receptor agonist or antagonist activity". The examiner notes that the term "receptor agonist activity" is defined on page 33 of the specification. The term "receptor antagonist activity" is also defined on pages 33 and 34 of the specification. The definitions on these pages of the specification and the skill of the art would lead one to understand that "receptor agonist activity" is the ability to bind to a native cell surface receptor and, thereby, mediate signal production by the receptor. On the other hand, "receptor antagonist activity" is the ability to bind to a native cell surface receptor without mediating signal production by the receptor, thus preventing the biological activity of native interferon (see page 33, lines 17-25). As the specific activity being referred to is now clearly set forth in the claim and clearly defined by the specification, this rejection has now been

obviated. Reconsideration and withdrawal thereof is respectfully urged.

Claims 1-28 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite in the recitation of "functional derivatives". The examiner states that applicants have not described what actions are considered deriving and what actions are excluded. This rejection is respectfully traversed.

The term "functional derivatives" is fully defined in the present specification on page 30. Functional derivatives are chemical derivatives prepared from the functional groups which occur as side chains on the residues of the N- or C-terminal groups by means known in the art. Examples include aliphatic esters, amides, N-acyl derivatives, O-acyl derivatives, etc. The specification clarifies that the term "derivatives" includes only those derivatives that do not change one amino acid to another of the twenty commonly occurring natural amino acids. It is not understood what part of this detailed definition is indefinite. Furthermore, this term is commonly used in patent claims. Indeed, a search of the Patent and Trademark Office database shows that there are 399 patents with "functional derivative" or "functional derivatives" in a claim. Attached hereto are the front page, the claims and the page of the specification defining

"functional derivative" of seven of these patents, which show that patents with definitions of functional derivative that are very similar to that set forth in the present specification have issued with the term "functional derivative" in the claim, thereby proving that it is not inherently indefinite. The attached patents include patents 5,462,731; 5,491,129; 5,908,827; 5,976,543; 6,110,746; 6,136,309; and 6,180,103. If the examiner prefers, applicants would be willing to insert into the claim language similar to that used in the claims of the '746 and '103 patents, i.e.:

> wherein said functional derivatives consist of chemical modifications to amino acid side chains and/or the carboxyl and/or amino moieties of said peptides

or

> functional derivatives thereof prepared from the functional groups which occur as side chains on the residues thereof or the N- or C-terminal groups thereof.

In view of the clear definition in the specification, Reconsideration and withdrawal of this rejection are respectfully urged.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made".

It is submitted that all the claims now present in the case clearly define over the references of record and fully comply with 35 U.S.C. §112. Reconsideration and allowance are, therefore, earnestly solicited.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By _____
Roger L. Browdy
Registration No. 25,618

RLB:rd
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528
F:\,S\Ser1\Tepper1A\Pto\AmendmentC.doc



C

**Version with Markings to Show Changes Made**

Claims 1, 10, 22, 23, and 25-28 have been amended as follows:

1 (~~Amended~~Twice-amended). A method for prolonging the *in vivo* effect of Type I interferon (IFN), comprising:

administering to a patient in need of Type I IFN therapy a complex of Type I IFN and a subunit of the human interferon α/β receptor (IFNAR) which is capable of binding to the Type I IFN of the complex, in an amount effective to provide such IFN therapy,

wherein said Type I IFN has a sequence consisting essentially of the sequence of

a) a native Type I IFN;

b) a fragment of a) which has Type I IFN ~~biological~~ receptor agonist or antagonist activity;

c) a variant of a) or b) which has at least 70% sequence identity with a) or b) and which has Type I IFN ~~biological~~ receptor agonist or antagonist activity; or

d) a variant of a) or b) which is encoded by a DNA sequence which hybridizes to the complement of the native DNA sequence encoding a) or b) under moderately stringent conditions and which has Type

I IFN ~~biological~~ receptor agonist or antagonist activity; ~~or~~

~~e)~~ or a salt or functional derivative of a), b), c), or d) which has Type I IFN ~~biological~~ receptor agonist or antagonist activity; and

wherein said IFNAR has a sequence consisting essentially of the sequence of

~~f~~e) a native human IFNAR polypeptide chain;

~~g~~f) a fragment of ~~f~~e) which has IFNAR ~~biological~~ receptor agonist or antagonist activity;

~~h~~g) a variant of ~~f~~e) or ~~g~~f) which has at least 70% sequence identity with ~~f~~e) or ~~g~~f) and which has IFNAR ~~biological~~ receptor agonist or antagonist activity;

~~i~~h) a variant of ~~f~~e) or ~~g~~f) which is encoded by a DNA sequence which hybridizes to the complement of the native DNA sequence encoding ~~f~~e) or ~~g~~f) under moderately stringent conditions and which has IFNAR biological activity; ~~or~~

~~j)~~ or a salt or functional derivative of ~~f~~e), ~~g~~f), ~~h~~g), or ~~i~~h) which has IFNAR biological activity,

with the proviso that when said Type I IFN and said IFNAR are administered separately and said complex is formed

*in vivo*, the amount of IFNAR administered is an amount effective to prolong the *in vivo* effect of the Type I IFN.

10 (~~Amended~~Twice-amended). An isolated molecule comprising a complex of a Type I interferon (IFN) and a subunit of the human interferon α/β receptor (IFNAR) which is capable of binding to the Type I IFN of the complex, in which said Type I IFN is bound to said IFNAR by a covalent bond or a peptide bond,

wherein said Type I IFN has a sequence consisting essentially of the sequence of

a) a native Type I IFN;

b) a fragment of a) which has Type I IFN ~~biological~~ receptor agonist or antagonist activity;

c) a variant of a) or b) which has at least 70% sequence identity with a) or b) and which has Type I IFN ~~biological~~ receptor agonist or antagonist activity; or

d) a variant of a) or b) which is encoded by a DNA sequence which hybridizes to the complement of the native DNA sequence encoding a) or b) under moderately stringent conditions and which has Type I IFN ~~biological~~ receptor agonist or antagonist activity; ~~or~~

~~c)~~ or a ~~salt or~~ functional derivative of a), b), c), or d) which has Type I IFN ~~biological~~ receptor agonist or antagonist activity; and

wherein said IFNAR has a sequence consisting essentially of the sequence of

~~f~~e) a native human IFNAR polypeptide chain;

~~g~~f) a fragment of ~~f~~e) which has IFNAR biological activity;

~~h~~g) a variant of ~~f~~e) or ~~g~~f) which has at least 70% sequence identity with ~~a~~e) or ~~b~~f) and which has IFNAR biological activity; or

~~i~~h) a variant of ~~f~~e) or ~~g~~f) which is encoded by a DNA sequence which hybridizes to the complement of the native DNA sequence encoding ~~f~~e) or ~~g~~f) under moderately stringent conditions and which has IFNAR biological activity; ~~or~~

~~j)~~ or a salt or functional derivative of ~~f~~e), ~~g~~f), ~~h~~g), or ~~i~~h) which has IFNAR biological activity.

22 (Amended). A pharmaceutical composition consisting essentially of a pharmaceutically acceptable carrier and a complex of a Type I interferon (IFN) and a subunit of the human interferon α/β receptor (IFNAR) which is capable of binding to the type I IFN of the complex,

wherein said Type I IFN has a sequence consisting essentially of the sequence of

a) a native Type I IFN;

b) a fragment of a) which has Type I IFN ~~biological~~ receptor agonist or antagonist activity;

c) a variant of a) or b) which has at least 70% sequence identity with a) or b) and which has Type I IFN ~~biological~~ receptor agonist or antagonist activity; or

d) a variant of a) or b) which is encoded by a DNA sequence which hybridizes to the complement of the native DNA sequence encoding a) or b) under moderately stringent conditions and which has Type I IFN ~~biological~~ receptor agonist or antagonist activity; ~~or~~

~~e)~~ or a salt or functional derivative of a), b), c), or d) which has Type I IFN ~~biological~~ receptor agonist or antagonist activity; and

wherein said IFNAR has a sequence consisting essentially of the sequence of

~~f~~e) a native human IFNAR polypeptide chain;

~~g~~f) a fragment of ~~f~~e) which has IFNAR ~~biological~~ receptor agonist or antagonist activity;

~~h~~g) a variant of ~~f~~e) or ~~g~~f) which has at least 70% sequence identity with ~~f~~e) or ~~g~~f) and which has IFNAR ~~biological~~ receptor agonist or antagonist activity; or

~~i~~h) a variant of ~~f~~e) or ~~g~~f) which is encoded by a DNA sequence which hybridizes to the complement of the native DNA sequence encoding ~~f~~e) or ~~g~~f) under moderately stringent conditions and which has IFNAR ~~biological~~ receptor agonist or antagonist activity; ~~or~~

~~j)~~ or a salt or functional derivative of ~~f~~e), ~~g~~f), ~~h~~g), or ~~i~~h) which has IFNAR biological activity.

23 (Amended). A method for potentiating the biological effects of Type I interferon (IFN), comprising:

administering to a patient in need of Type I IFN therapy a subunit of the human interferon α/β receptor (IFNAR) which is capable of binding to the Type I IFN to be potentiated, in an amount effective to provide such IFN therapy,

wherein said IFNAR has a sequence consisting essentially of the sequence of

a) a native human IFNAR polypeptide chain;

b) a fragment of a) which has IFNAR ~~biological~~ receptor agonist or antagonist activity;

c) a variant of a) or b) which has at least 70% sequence identity with a) or b) and which has IFNAR ~~biological~~ receptor agonist or antagonist activity; or

d) a variant of a) or b) which is encoded by a DNA sequence which hybridizes to the complement of the

native DNA sequence encoding a) or b) under moderately stringent conditions and which has Type I IFN ~~biological~~ receptor agonist or antagonist activity; ~~or~~

~~e)~~ or a salt or functional derivative of a), b), c), or d) which has IFNAR ~~biological~~ receptor agonist or antagonist activity.

25 (Amended). A method in accordance with claim 1, wherein said native human IFNAR polypeptide chain of ~~f~~e) is the extracellular domain of a native human IFNAR polypeptide chain.

26 (Amended). A molecule in accordance with claim 10, wherein said native human IFNAR polypeptide chain of ~~f~~e) is the extracellular domain of a native human IFNAR polypeptide chain.

27 (Amended). A pharmaceutical composition in accordance with claim 22, wherein said native human IFNAR polypeptide chain of ~~f~~e) is the extracellular domain of a native human IFNAR polypeptide chain.

28 (Amended). A method in accordance with claim 3, wherein said native human IFNAR polypeptide chain of ~~a~~e) is the extracellular domain of a native human IFNAR polypeptide chain.